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Reductions in radiographic progression in early RA over 25-years: changing contribution from RF in 2 multi-centre UK inception cohorts

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Objectives: To assess 5-year progression of erosions and Joint Space Narrowing (JSN), and their associations with RF status in two large, multi-centre early-RA cohorts spanning 25-years.

Methods: Radiographic joint damage was recorded using the Sharp/van der Heijde (SvdH) method in the Early RA Study (ERAS) 1986-2001, and the Early RA Network (ERAN) 2002-2013. Mixed-effects negative-binomial regression estimated changes in radiographic damage over 5-years, including erosions and JSN separately. Rheumatoid Factor (RF), along with age, sex and baseline markers of disease activity were controlled for.

Results: 1,216 patients from ERAS and 446 from ERAN had radiographic data. Compared to ERAS, ERAN patients had a lower mean total SvdH score at baseline (ERAN=6.2 vs. ERAS=10.5, p<0.001), and mean annual rate of change (ERAN=2.5 vs. ERAS=6.9 per year, p<0.001). 74% of ERAS and 27% of ERAN patients progressed ≥5 units. Lower scores at baseline in ERAN were largely driven by reductions in JSN (ERAS=3.9 vs. ERAN=1.2, p<0.001), along with erosions (ERAS=1.9 vs. ERAN=0.8, p<0.001). RF was associated with greater progression in each cohort, but the absolute difference in mean annual rate of change for RF positive patients was substantially higher for ERAS (RF+= 8.6 vs. RF-= 5.1, p<0.001), relative to ERAN (RF+= 2.0 vs. RF-= 1.9, p=0.855).

Conclusion: Radiographic progression has significantly reduced between the two cohorts, associated with lower baseline damage and other factors, including changes in early DMARD use. The impact of RF status as a prognostic marker of clinically

meaningful change in radiographic progression has markedly diminished in the context of more modern treatment.

Significance and Innovations

- Radiographic damage at baseline and progression over the first 5-years has reduced over the last 25-years.
- Joint space narrowing is the main driver for reductions in radiographic progression early after diagnosis, with reductions in erosions contributing later in the disease course.
- RF+ RA remains a significant predictor of increased radiographic damage, however in the context of overall reductions, it is no longer associated with clinically-meaningful changes in radiographic damage.

Published literature has suggested that the incidence of Rheumatoid Arthritis (RA) has declined over the last three decades[1–9]. This corresponds with reports of declines in disease activity[10,11] , functional disability[12,13], orthopaedic surgery[14] and radiographic progression[12,15,16].

While the causes are not entirely clear, it is hypothesised that these declines in disease severity are related to widespread changes in treatment strategies during the 1990s[17]. Data from randomised controlled trials (RCTs) have demonstrated that early initiation of conventional synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) can significantly improve patient outcomes, particularly the increased use of methotrexate in combination with other DMARDs[18–21], and indeed biologic DMARDs[22–25].

Radiographic joint damage is often used in RCTs as a primary outcome, and has been shown to be strongly related to levels of functional disability[26] and disease activity[27]. Although commonly expressed as a global score[28], radiographic joint damage comprises two main components, erosions and joint space narrowing (JSN). While related, they are thought to be the result of two distinct pathophysiological mechanisms[29,30]. Possible causes of erosive joint destruction are the products of invading synovium into the boney structures of the joints, and increased osteoclast activity[31]. In contrast, JSN has been hypothesised to reflect cartilage damage as a result of metalloproteinases, which are upregulated by pro-inflammatory

cytokines[32]. JSN is common to a range of pathologies, including osteoarthritis (OA), which is a common comorbid condition in people with RA[33]. Despite this, much of the focus of longitudinal data concerning radiographic damage has reported the combination of these two processes as one composite score[29,30], for example using the radiographic scoring methods of Ratingen or Larsen, that lack the ability to distinguish progression of erosions and JSN as separate domains[12,15,16].

Further still, rheumatoid factor (RF) status has been strongly associated with worse radiographic progression[34–36], however, to date no study has looked at whether the relative strength of this association has changed given the wider demographic changes seen in many other aspects of RA, including disease severity. It might be hypothesised that radiographic measures of RA will show significant changes given declines in disease activity, but whether previously demonstrated risk factors for progression continue to be influential remains unclear.

This study therefore aims to investigate long-term radiographic progression by comparing data from two UK, multi-centre inception cohorts, the Early RA Study (ERAS), which collected patient data from 1986-2001, and the Early RA Network (ERAN), which collected data from 2002-2013. Specifically, this study 1) compares the total SvdH, erosion and JSN scores at baseline and the rate of progression over the first 5-years between the two cohorts, and 2) estimates the association between RF status and radiographic damage at baseline and progression over the first 5-years in ERAS and ERAN.

Patients and Methods

The data used for this study were collected from two longitudinal inception cohorts, ERAS and ERAN. ERAS recruited 1,465 patients from 9 centres across the UK between 1986-2001, while ERAN recruited 1,236 patients from 25 centres between 2002 and 2013. Two centres recruited to both cohorts. All patients had a confirmed diagnosis of RA and were recruited within 3 years of symptom onset, typically prior to conventional DMARD initiation. Maximum follow-up for ERAS was 25 years (median 10 years) and for ERAN was 11 years (median 3 years). All patients were treated based on standard clinical practice of the time.

Standard clinical, laboratory and radiographic data were collected at baseline, 3 to 6 months, 12 months, and then yearly thereafter. These included the original three variable 44-joint Disease Activity Score (DAS) for ERAS and the DAS28 for ERAN, the Health Assessment Questionnaire (HAQ), Rheumatoid Factor Positivity and haemoglobin level. To enable comparison of disease activity across the two cohorts, the original DAS in ERAS was converted to DAS28 using the formula DAS28 = (1.072*DAS) + 0.938[37].

Radiographic scoring

Structural joint damage was assessed from plain radiographs using the SvdH scoring method[38]. All 32 centres collected yearly plain x-rays of hands and feet. Radiographs from all 9 centres recruiting from ERAS, and 7/25 (28%) centres from ERAN scored films using the SvdH method.

The SvdH rates radiographic damage based on the prevalence and severity of the erosions in 32 joints in the hands and 12 joints in the feet, and the prevalence and

severity of JSN in 30 joints in the hands and 12 joints in the feet. Each joint was rated from 0-5 (or 0-10 for erosions in the joints of the feet) giving a maximum score of 280 for the erosion score and 168 for the JSN score. These scores were combined to give a total SvdH score ranging from 0 to 448.

One person (KJ) scored the radiographs for ERAS, while another person (DMcW) scored the radiographs for ERAN. Each scorer rated the radiographs in chronological order. To assess agreement between the two, both scored a random sub-sample of thirty-nine radiographs from twenty patients from the ERAS cohort at two time-points (baseline and 5 years). An Intra-class Correlation Coefficient (ICC) of 0.95 (95% confidence intervals 0.90-0.97) was calculated for the erosion score, and 0.98 (95% CI 0.95-0.99) calculated for both the JSN score and total SvdH score. The ICC is an estimate of the proportion of the total variability in ratings for the sample that are due to variability between x-rays, rather variability within x-rays between readers. The high values in our assessment of agreement confirm the risk of systematic bias due to two readers is low, and as such the level of agreement acceptable for the comparison of trends over time.

Statistical analysis

To assess differences in the use of first-line conventional DMARDs between the two cohorts, the cumulative incidence of time to first DMARD within the first 12 months from first outpatient appointment was estimated. This was estimated for any DMARD use, as well as separate estimates for the two most commonly used first-line DMARDS, methotrexate and sulphazalasine.

The skewed distributions of radiographic scores derived by the SvdH method renders linear regression inappropriate[39]. Generalised linear regression with a negative-binomial distribution, henceforth negative binomial regression (NBR), was found to achieve best fit to the data, compared with linear and Poisson distributions. Mixed-effects NBR (MENBR) models allowed for the longitudinal structure of the data to be modelled appropriately, whereby random intercept and time slope parameters were estimated. Cohort membership (either ERAS or ERAN) was the main covariate of interest. Baseline scores, along with yearly measures of SvdH were used in the models to estimate rates at presentation and over the 5-year follow-up. Missing data is inherent in longitudinal studies. To probe potential selection bias based on the availability of radiographs, baseline characteristics of those with and without radiographic data were compared. Furthermore, protecting against confounding due to missing longitudinal data, mixed-effects models use full information maximum likelihood making use of all available data under the *missing at random* assumption, so that all patients with data are included.

Time was defined as years from enrolment and was included as a continuous variable with a random slope to allow for the estimation of the annual rate of progression for each patient. RF status was the secondary covariate of interest and entered as a main effect, along with a three-way interaction term with cohort and time to allow for progression rates to be estimated separately by RF status for each cohort. Sensitivity analysis, which substituted cohort membership for year of diagnosis in the model, was used to investigate the effect of calendar year on long-term radiographic progression. Sex, age, DAS28, HAQ, low Hb (<12 for females /<13 for males), months from symptom onset to first rheumatology visit, steroid use prior

to first assessment and DMARD use within first 12-months were all entered into the model to control for any potential confounding effects.

Exponentiated regression coefficients of an NBR model are incidence rate ratios (IRR), which are interpreted as the relative increase in the log-count of the dependent variable (i.e. the SvdH score) given a one-unit increase in the respective covariate (e.g. age). To aid interpretation, the results from the models were also expressed as an absolute change in the SvdH score using the estimated mean SvdH, along with 95% Confidence Intervals [95% CI]. This allowed for a more direct interpretation of the effect that each factor had in terms of absolute difference in SvdH units, the percentage of maximum possible damage, and annual progression greater than the minimum clinically important difference of 5 units[40].

These models were estimated separately for the total SvdH score, JSN and erosion score. All analyses were conducted using Stata (version 14; StataCorp LP, USA).

Results

Of the 2,701 total patients recruited, 1,662 had SvdH data: 1,216 from ERAS and 446 from ERAN. The demographic and baseline clinical characteristics of both ERAS and ERAN patients, including only those with radiographic data, are shown in Table 1. Reasons for missing radiographic data included loss of records, unreadable radiographs and loss to follow-up. Patients from ERAS were marginally younger at presentation and had higher DAS28, ESR, HAQ and were more likely to be anaemic at baseline, but the median time from first symptom to first visit was the same. Patient characteristics with recorded radiographic data were similar to the total patients in their respective cohort.

Table 1 - Summary Statistics for each Cohort

Differences in treatment strategies between the two Cohorts

For all DMARDs, ERAS reported a 12-month cumulative incidence of 71.6% [95%CI 69.2-73.8] and for ERAN 95.3% [95%CI 93.9-96.4] (See Figure 1). The 12-month cumulative incidence of sulfasalazine (SSZ) use was higher in ERAS (55% [95%CI 52.4-57.5]) than ERAN (33.1% [95%CI 30.4-35.8]), while methotrexate (MTX) use was substantially lower in ERAS (1.4% [95%CI 0.9-2.1]) compared to ERAN (52.1% [95%CI 49.2-55.0]).

Figure 1. 12-month Cumulative Incidence of DMARD use for ERAS and ERAN

Radiographic progression rates of ERAS and ERAN

For the MENBR analysis a total of 1,508 patients contributing 5,430 observations (mean observations per patient = 3.6) were included. Overall, the ERAN cohort exhibited a 41% lower total SvdH score at baseline compared to ERAS (IRR 0.59 [95%CI 0.50-0.70], p<0.001), along with a 65% slower annual rate of progression over the first 5-years (IRR 0.35 [95%CI 0.24-0.47], p<0.001) (See Figure 2A). The differences in absolute and relative scores for both cohorts are shown in Table 2. When expressed as a proportion of maximum possible damage, the estimated values indicated an increase of 1.5% [95%CI 1.4-1.7] per year for ERAS and 0.6% [95%CI 0.4-0.7] per year for ERAN. The total proportion of patients who had annual progression estimated to be greater than the MCID (≥5 SvdH units) was 74% for ERAS and 27% for ERAN. Sensitivity analysis modelling calendar year, rather than cohort, indicated that each additional calendar year decreased the risk of radiographic progression by 3% (IRR 0.97 [95%CI 0.96-0.99], p<0.05). Additional sensitivity analysis also

controlling for baseline BMI found that while increased BMI at baseline was protective of increased radiographic damage over the first 5 years, it did not alter the main cohort effect (results not shown).

Table 2. Mean and relative difference in baseline level and annual rate of progression for Total SvdH, JSN and erosion scores between 1986-2001 (ERAS) and 2002-2013 (ERAN). Estimates based on fixing the values of the covariates to the sample means. Controlling covariates = age, sex, RF status, baseline DAS28, baseline HAQ, low Hb (<12/13) at baseline, months from symptom onset to first rheumatology visit, steroid use prior to first assessment and DMARD use

Similar results were seen for the JSN score, with ERAN participants displaying lower scores at baseline (IRR 0.49 [95%CI 0.41-0.58], p<0.001) and a slower annual rate of progression over the first 5-years compared to ERAS (IRR 0.31 [95%CI 0.21-0.42], p<0.001) (See Figure 2B).

For the erosion score, the score at baseline was similar for both cohorts (IRR 0.94 [95%CI 0.73-1.19], p=0.593), however, ERAN exhibited a slower annual rate of progression over the first 5-years compared to ERAS (IRR 0.43 [95%CI 0.25-0.61], p<0.001) (See Figure 2C). See Table 2 for absolute and relative changes in both JSN and erosion scores between the two cohorts.

Figure 2 - Progression of A) Total SvdH, B) JSN and C) Erosion score for 1986-2001 (ERAS) and 2002-2013 (ERAN)

Association of RF status with radiographic progression in ERAS and ERAN

The absolute and relative difference in total SvdH scores for RF+ and RF- patients in both cohorts are given in Table 3 and displayed graphically in Figure 3. For the total SvdH score, RF+ RA was not significantly associated with increased radiographic damage at baseline, compared to RF- RA, in either ERAS or ERAN. RF+ RA was associated with a 70% increased annual rate of progression, compared to RF- RA, in

ERAS, which was statistically significant. The annual rate of progression for RF+ RA, compared to RF- RA, in ERAN was increased by 9%, which was not significant. This relates to decreases in the relative impact of RF+ RA on the annual rate of progression of 36% for ERAN compared to ERAS, which although considerable was non-significant (IRR 0.64 [95%CI 0.29-1.07], p=0.224). This related to the proportion of RF+ patients with an annual progression greater than the MCID of 80% for ERAS and just 29% for ERAN.

Investigation of the association between RF+ RA in both the cohorts for the separate JSN and erosion score indicated similar results to the total SvdH (See Supplementary Material 1).

Figure 3 - Progression of Total SvdH score for ERAS and ERAN stratified by RF status

Table 3. Mean and relative difference in baseline level and annual rate of progression for Total SvdH based on RF status between 1986-2001 (ERAS) and 2002-2013 (ERAN). Estimates based on fixing the values of the covariates to the sample means. Controlling covariates = age, sex, baseline DAS28, baseline HAQ, low Hb (<12/13) at baseline, months from symptom onset to first rheumatology visit, steroid use prior to first assessment and DMARD use

Discussion

The findings from the present study indicate that patients with early RA with onset from 2002-2013 (ERAN) had significantly lower baseline and annual rates of radiographic progression compared to those with onset from 1986-2001 (ERAS). Examination of the separate erosion and JSN scores indicate that the reduction in the total SvdH score was largely driven by less JSN. Strikingly, the strong association of RF status and increased radiographic progression in the earlier time period (ERAS) was markedly diminished in the later time period (ERAN). Those with RF+ RA from

2002-2013 had markedly better radiographic outcomes at 5 years than those with RF- RA in 1986-2001.

Previous research has indicated that a change of 5 SvdH units indicates a minimal clinically important difference[40,41], therefore a difference of 5 units per year for ERAN compared to ERAS on total SvdH score observed in this study demonstrates not only a statistically significant change in progression, but also a clinically meaningful reduction. Whereas 74% of patients in the earlier cohort progressed on average ≥5 units per year over the 5-year period of follow-up considered, just 27% of patients in the later cohort did.

Our data extend previous findings of reductions in radiographic damage in RA over recent decades [12,15,16]. There are two plausible explanations for these findings, both of which are likely to contribute to the reduction in radiographic damage over time. Firstly, RA may have become milder, and secondly, earlier more intensive treatment may have improved disease outcomes. Our models adjusted for disease severity at baseline, but it remains possible that lower rates of progression in the more recent cohort reflect milder disease. This is supported by the observation of lower SvdH scores in ERAN compared to ERAS at baseline, prior to DMARD initiation, even though the median time from first symptom to first visit was the same for both cohorts. However, the reduction in radiographic progression is likely to also reflect improvements in the treatment of RA, given the earlier and increased use of methotrexate as the first line DMARD observed in ERAN in this study, which is in line with other reports [12,15,16,36]. Increasing evidence from RCTs also support the hypothesis that early, intensive treatment has an important effect on reducing radiographic progression[42–46].

Separate investigation of the erosion and JSN components of radiographic damage scores showed that JSN was the primary driver for the overall reductions seen in the total SvdH score between the two cohorts. This finding reiterates the importance of reporting both the erosion and JSN score separately in clinical trials. Data from ASPIRE show that more patients with early RA have either erosions alone (8.5%) or JSN alone (4.4%), than both (3.7%) at baseline visit[30], and that JSN may be more strongly associated with irreversible disability[29]. Despite this, the separate scores are still rarely reported[28]. If early treatment with MTX was the primary cause for the reduction in total SvdH in ERAN, this could indicate that the mechanism by which this is achieved is through the reduction of JSN and preservation of the surrounding cartilage. However, what is not clear is whether the JSN is directly attributable to RA JSN, or OA JSN. A high prevalence of radiographic OA has been documented at baseline in the ERAN cohort in the hands and feet, indicating that high levels of comorbid OA could potentially confound any radiographic assessment of RA[33]. High JSN scores are strongly associated with increased severity of OA osteophytosis and OA JSN[47]. More studies are needed to quantify the exact effect that co-morbid OA could be having on RA radiographic scoring.

Seropositive RA has been consistently associated with increased radiographic damage[35,36]. This study also found that RF+ RA was highly associated with increased radiographic progression. However, when investigating the absolute change in radiographic score between RF+ and RF- patients across the two cohorts, RF+ patients between 2002-2013 no longer represented a patient sub-group with clinically meaningful increases in radiographic progression, at least within the first 5-years of disease. Aletaha et al.[48] analysed the effect of seropositive status on

radiographic progression and found seropositive patients displayed higher radiographic progression, compared to seronegative patients[39,49]. The estimated change in median SvdH score of 0.6 units per year for seropositive over that of seronegative patients provides an estimate similar to this study.

Many RCTs are restricted to seropositive patients only, and previous research has not focused on the effect of seropositivity in the context of reduced radiographic progression in more recent years. The two long-term observational cohorts examined in this study provide a 'real-world' account of patients typically seen in secondary care, and the high patient numbers over the full 5-year follow-up also provides a unique opportunity to provide precise estimates using the modelling techniques outlined[39]. The use of the SvdH score also provides a first look at the two principle components of radiographic damage, erosions and JSN, in detail. Further data from observational studies are needed to ascertain whether reductions in radiographic progression have also resulted in the diminished association with RF status, particularly in the context of anti-CCP seropositive RA, which could be more predictive of radiographic progression when compared to RF[36,50,51].

Our research is subject to a number of limitations inherent in cohort studies. Recruiting centres were hosted by enthusiastic clinicians within the UK and, although they might not necessarily reflect people with RA in other contents, or subjected to different treatment regimens, the multicentre recruitment for these cohorts from district general hospitals is likely to be representative of people with RA in the UK. Radiographs were not available for all participants, and it is possible that those with more severe disease were more likely to have x-rays, increasing the risk of selection bias in our study. However, baseline variables indicated minimal differences

between the whole cohorts, and those for whom radiographic data were available. The impact of such a selection bias would overestimate rates of progression, particularly for ERAN, where data were less complete; hence our estimates should be treated as conservative.

This study provides further evidence into the marked reduction in radiographic damage over the last 25-years, while providing accurate, quantified estimates of the extent of that reduction. JSN was the major driver for the overall reductions seen, and highlights the importance of investigating JSN and erosions separately when investigating radiographic damage. Advances in treatment are likely to be the main cause for the decline, and adequate DMARD treatment might remove the predictive value of RF status for radiographic progression in early RA. Further research should seek other predictors and mediators if residual radiographic progression despite DMARD treatment is to be halted. The impact of these reductions on patients of varying disease severity, and whether these reductions have an impact on improved long-term functional disability will be crucial in fully realising the impact of these results on clinical care.

Declarations

The authors declare no conflicts of interest.

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Tables and Figures

Table 1 - Summary Statistics for each Cohort

	ERAS		Total	ERAN		Total	**ERAS+ERAN**	
	Total n=1465	With SvdH n=1216	Missing n(%)	Total n=1236	With SvdH n=446	Missing n(%)	**Total n=2701**	**With SvdH n=1662**
Demographics								
Year of Recruitment	1986-2001	1986-2001	0 (0)	2002-2013	2002-2013	0 (0)	1986-2013	1986-2013
Age at Onset (Mean (SD))	55.3 (14.6)	54.9 (14.5)	0 (0)	57.1 (14)	58 (13.5)	0 (0)	56.1 (14.4)	55.7 (14.3)
Female (%)	66	66	0 (0)	68	65	0 (0)	67	65
Clinical Markers								
Rheumatoid Factor + (%)	63	64	9 (0.1)	60	61	142 (11)	62	63
Baseline DAS (Mean (SD))	6.32 (1.33)	6.32 (1.33)	13 (0.1)	4.53 (1.58)	4.5 (1.64)	46 (4)	5.51 (1.7)	5.84 (1.62)
Baseline ESR (Median (IQR))	37 (44)	38 (44)	7 (0.1)	24 (29)	21 (28)	183 (15)	30 (39)	34 (41)
Baseline HAQ (Mean (SD))	1.15 (0.8)	1.15 (0.8)	5 (0.1)	1.08 (0.8)	1.03 (0.8)	37 (3)	1.12 (0.8)	1.12 (0.8)
Baseline Anaemia (%)	41	42	5 (0.1)	28	24	32 (3)	35	37
Months from symptom onset to First Visit (Median (IQR))	6 (7)	6.5 (7)	0 (0)	6 (8)	6 (8)	91 (7)	6 (8)	6 (8)
Treatment								
DMARD use (12 months (%))	73	73	38(3)	96	98	276(22)	82	79
Methotrexate	2	2		57	64		24	17
Sulphazalzine	55	55		31	28		46	49
Hydrochloroquine	14	13		3	3		9	11
Other	2	2		4	2		3	2

Numbers represent means (SD), medians (IQR) and proportions were used where indicated.
SvdH = Sharp/van der Heijde, DAS=Disease Activity Score-28, ESR=Erythrocyte Sedimentation Rate, HAQ = Health Assessment Questionnaire.

Table 2. Mean and relative difference in baseline level and annual rate of progression for Total SvdH, JSN and erosion scores between 1986-2001 (ERAS) and 2002-2013 (ERAN). Estimates based on fixing the values of the covariates to the sample means. Controlling covariates = age, sex, RF status, baseline DAS28, baseline HAQ, low Hb (<12/13) at baseline, months from symptom onset to first rheumatology visit, steroid use prior to first assessment and DMARD use

Estimated means	ERAS	ERAN	Absolute Difference	Relative Difference (IRR) [95% CI]	P-Value
Total SvdH at baseline	10.5	6.2	4.3	**0.59 [0.50-0.70]**	**<0.001**
Total SvdH annual rate	6.9	2.5	4.5	**0.35 [0.24-0.47]**	**<0.001**
JSN score at baseline	7.4	3.6	3.8	**0.49 [0.41-0.58]**	**<0.001**
JSN score annual rate	3.9	1.2	2.7	**0.31 [0.21-0.42]**	**<0.001**
Erosion score at baseline	1.8	1.7	0.1	0.94 [0.73-1.19]	0.593
Erosion score annual rate	1.9	0.8	1.1	**0.43 [0.25-0.61]**	**<0.001**

Table 3. Mean and relative difference in baseline level and annual rate of progression for Total SvdH based on seropostive (RF+) status between 1986-2001 (ERAS) and 2002-2013 (ERAN). Estimates based on fixing the values of the covariates to the sample means. Controlling covariates = age, sex, baseline DAS28, baseline HAQ, low Hb (<12/13) at baseline, months from symptom onset to first rheumatology visit, steroid use prior to first assessment and DMARD use

		RF-	RF+	Difference	Relative Difference (IRR) [95% CI]	P-Value
ERAS	Total SvdH at baseline	9.5	11	1.5	1.16 [1.00-1.35]	0.056
	Total SvdH Annual rate	5.1	8.6	3.6	**1.70 [1.42-1.97]**	**<0.001**
ERAN	Total SvdH at baseline	6.0	6.2	0.2	1.04 [0.76-1.42]	0.811
	Total SvdH Annual rate	1.9	2.0	0.2	1.09 [0.51-1.67]	0.855

Figure 1. 12-month Cumulative Incidence of DMARD use for 1986-2001 (ERAS) and 2002-2013 (ERAN)

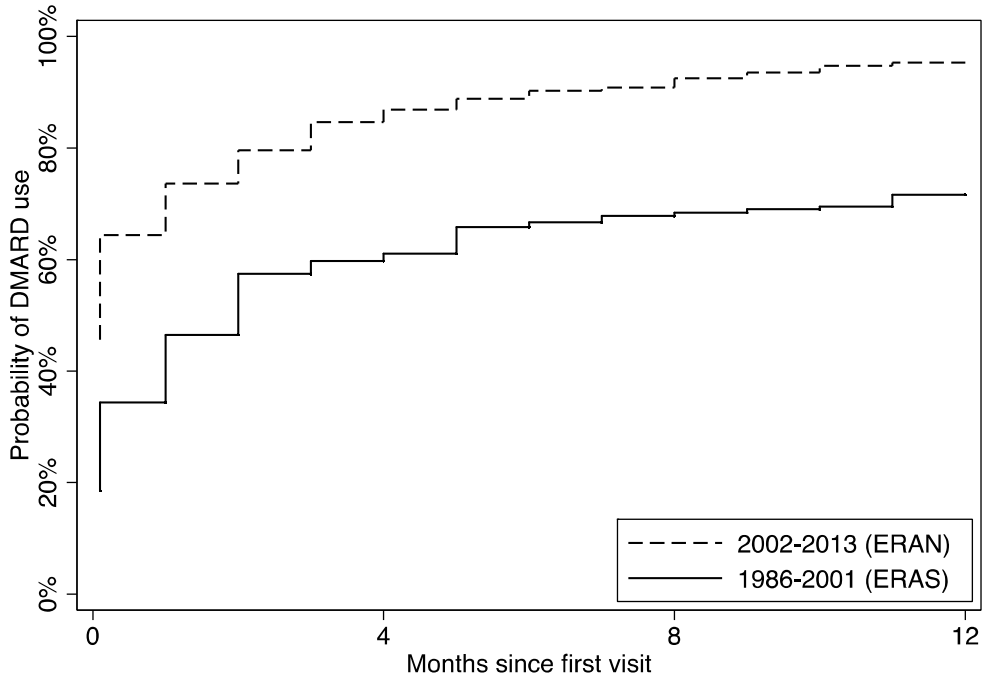


Figure 2 - Progression of A) Total SvdH, B) JSN and C) Erosion score for 1986-2001 (ERAS) and 2002-2013 (ERAN)

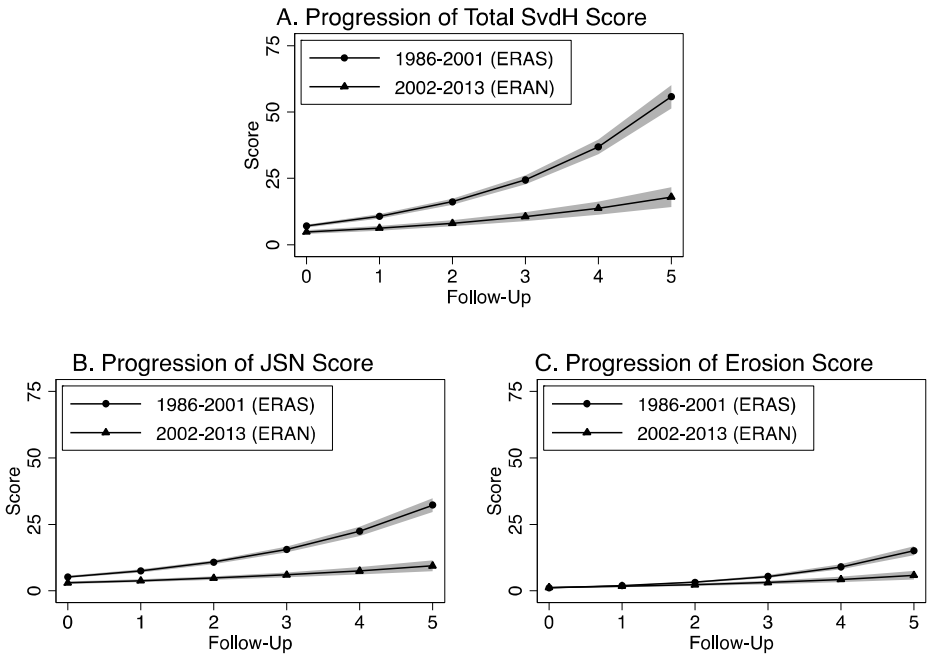
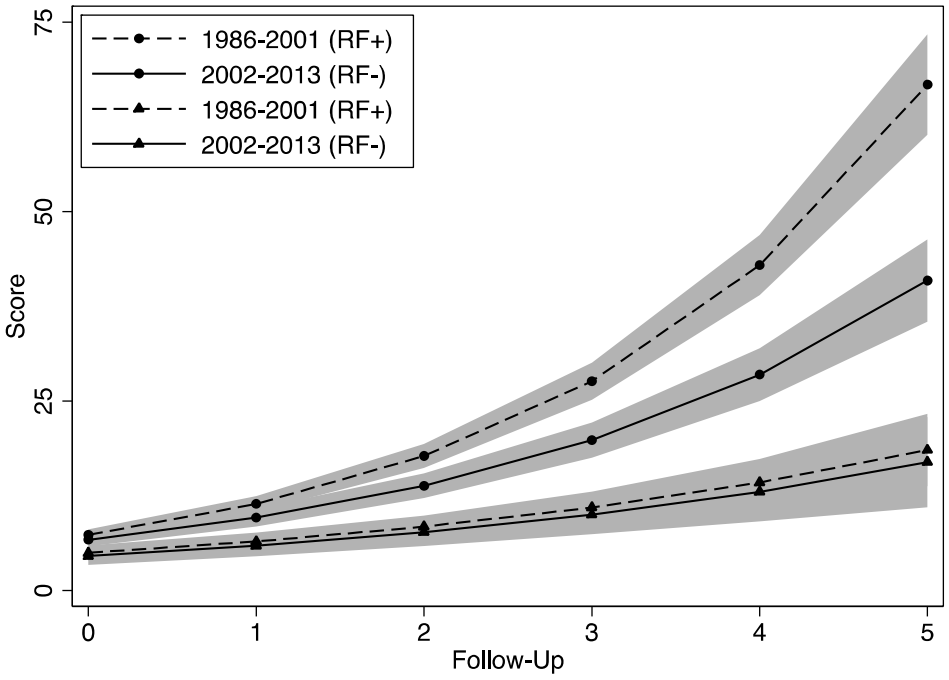


Figure 3 - Progression of Total SvdH score for 1986-2001 (ERAS) and 2002-2013 (ERAN) stratified by RF status



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Included in Title on page 1]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[See objectives and conclusion in abstract on page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Page 3 & 4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 2]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 4]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 4 & 5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Page 4]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 4 & 5]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Page 5]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 6]**
Study size	10	Explain how the study size was arrived at **[Page 4]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 5 & 6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Page 5 & 6]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Page 6]**
		(*c*) Explain how missing data were addressed **[Page 6]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[Page 6]**
		(*e*) Describe any sensitivity analyses **[N\A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 7]**
		(b) Give reasons for non-participation at each stage **[Page 7]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 7]**
		(b) Indicate number of participants with missing data for each variable of interest **[Page 7]**
		(c) Summarise follow-up time (eg, average and total amount) **[Page 8]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Page 8]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **[Page 8 & 9 & 10]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Page 8 & 9 & 10]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 9]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 12 & 13]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 11 & 12]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 12]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[N/A]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.